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Long-Term Mortality in Patients With Stroke of Undetermined Etiology

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Background and Purpose—The determination of stroke etiology is essential for planning treatment for stroke prevention. However, the etiology of stroke is undetermined in many patients.

Methods—During a 10-year period, consecutive patients with acute ischemic stroke were enrolled. The stroke etiology was determined based on the Trial of ORG 10172 in Acute Stroke Treatment classification. Long-term mortality and causes of death were identified using death certificates. The standardized mortality ratio was calculated to compare the mortality in patients with stroke and that in the general Korean population.

Results—In total, 3278 patients were enrolled and followed-up for a median of 3.4 years (interquartile range, 1.5–5.7). The stroke subtype was undetermined in 37% because of negative evaluation (21.2%), multiple causes (10.6%), and incomplete evaluation (4.8%). Poor functional outcome at 3 months (modified Rankin scale score >2) was more frequent in patients with an incomplete evaluation than in those with the other stroke subtypes (49.6% vs 24.5%; $P<0.001$). During follow-up, 781 patients (23.8%) died. The overall cumulative death rate was highest in patients with an incomplete evaluation (12.7% within 30 days, 25.5% within 1 year, and 35.7% within 3 years), followed by those with cardioembolism. Multivariate analysis after adjusting for covariates including initial stroke severity, the mortality of patients with an incomplete evaluation was second lowest after cardioembolism, whereas that in patients with a negative evaluation was low.

Conclusions—Long-term mortality in patients with an incomplete evaluation was quite high. Etiologic work-up helps to better define the stroke subtype and determine the prognosis. **(*Stroke*. 2012;43:2948-2956.)**

Key Words: brain infarction ■ etiology ■ outcomes ■ prognosis

See related article, p 2841.

Stroke patients have higher mortality than sex-matched and age-matched subjects who have not experienced a stroke.[1] During the past few decades, death rates from stroke have declined.[2,3] Some of the improvement in stroke mortality might be associated with improvement in acute care and long-term preventive treatment based on better evaluation of stroke etiologies, introduction of new medications, and aggressive control of risk factors.[4]

The ischemic stroke subtype is an important determinant of mortality in many prospective community-based studies and clinical trials.[5–9] Although determining the stroke mechanism is important for better treatment, the etiology of stroke remains undetermined in many patients,[10–12] because multiple etiologies are identified, physicians fail to identify the etiology despite extensive work-up, or evaluations are incomplete. Whereas stroke of undetermined etiology is common, long-term mortality in this group of patients remains unknown because most studies excluded patients with stroke of undetermined etiology because of the unclear nature.[8] Moreover, mortality in patients with stroke of undetermined etiology might differ according to the reasons for the undetermined etiology. In this study, we aimed to determine the long-term mortality of patients with stroke of undetermined etiology and to investigate the impact of stroke evaluation on long-term mortality in patients with acute ischemic stroke.

Subjects and Methods

Patients and Evaluation

Subjects for this study were drawn from consecutive patients with acute ischemic stroke who had been registered in the Yonsei Stroke Registry over a 10-year period (July 1997–June 2007). The Yonsei University Severance Hospital is a 2000-bed general hospital located in the western part of Seoul, the capital city of South Korea. Approximately 80% of stroke patients who are admitted to the study hospital are from Seoul and Gyeong-gi province, with ≈20 million inhabitants (Supplemental Figure I). The study hospital is 1 of many large hospitals in that area where patients can visit. The Yonsei Stroke Registry is a prospective hospital-based registry for patients

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with cerebral infarction or transient ischemic attack within 7 days after symptom onset.[10] During admission, all patients were thoroughly investigated for medical history, clinical manifestations, and presence of vascular risk factors. All registered patients underwent brain imaging studies including brain computed tomography (CT) or magnetic resonance imaging. An angiographic study using CT angiography, magnetic resonance angiography, or digital subtraction angiography was the standard evaluation tool. Every patient was evaluated with 12-lead electrocardiography (ECG), chest x-ray, lipid profile, and standard blood tests. For patients younger than 45 years old, additional blood tests for coagulopathy or prothrombotic conditions were performed.[13] Transesophageal echocardiography was a part of the standard evaluation, except in patients with decreased consciousness, impending brain herniation, poor systemic conditions, inability to accept an esophageal transducer because of swallowing difficulty or tracheal intubation, or lack of informed consent. Transthoracic echocardiography, heart CT, and Holter monitoring were performed in the selected patients.[13–15] A stroke unit was opened in the study hospital on December 2002. Since then, most patients have been admitted to the stroke unit and are monitored continuously with ECG during their stay in the stroke unit. Since July 2006, heart CT using multislice CT had been performed for the evaluation of the coronary artery, aorta, and heart. Patients were indicated for heart CT when they had at least one of the following: (1) presence of atherosclerosis in the intracranial or extracranial cerebral artery; (2) presence of ≥2 risk factors for coronary artery disease such as hypertension, diabetes mellitus, dyslipidemia, cigarette smoking, and central obesity; and (3) old age (males older than 45 years, females older than 55 years).[16]

Among the consecutive patients who had been registered in the prospective stroke registry, those with transient ischemic attack were excluded. When a patient was admitted more than twice because of recurrent strokes, only data for the first admission were used for this study. Initial stroke severity was determined by National Institute of Health Stroke Scale scores and score tertiles were used for the analysis. This study was approved by the Severance Hospital Institutional Review Board of Yonsei University Health System.

Stroke Subtype Classification and Clinical Variables

The stroke subtype was determined according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification.[17] Briefly, large artery atherosclerosis is defined when there is significant (≥50%) stenosis of the large artery relevant to the acute infarction. Cardioembolism is defined when there is at least 1 potential cardiac source of embolism, which is defined in the TOAST classification. A patient with a lacunar infarction should have 1 of the classic clinical lacunar syndrome and a relevant subcortical hemispheric or brain stem lesion with a diameter <1.5 cm. Stroke of other determined etiology includes patients with a rare cause of stroke, such as nonatherosclerotic vasculopathy, hypercoagulable state, and hematologic disorder. Stroke of undetermined etiology is defined when the mechanism of stroke cannot be determined and is further subdivided into undetermined etiology because of multiple causes identified, undetermined etiology attributable to negative evaluation despite extensive work-up, and undetermined etiology attributable to incomplete evaluation.[17] An incomplete evaluation was defined when the essential studies such as brain imaging (CT/magnetic resonance imaging for diagnosis and determining the stroke pattern), angiographic evaluation (CT angiography, magnetic resonance angiography, or digital subtraction angiography for determination of atherosclerosis or arteriopathy), or ECG (for detection of cardiac sources of embolism) were not performed. Echocardiographic studies were not considered as essential studies. The patients who lacked of any those essential studies were classified as those with undetermined etiology because of incomplete evaluation, except patients who did not undergo angiographic evaluation but had high-risk potential cardiac sources of embolism. They were classified as cardioembolism according to the original TOAST classification.[17] Therefore, typical patients with an incomplete evaluation were those who did not undergo evaluation for cerebral arteries and had not high risk for cardiac sources of embolism. Stroke classification was determined at weekly stroke conferences on the basis of a consensus among stroke specialists, and was prospectively entered into the computerized database.[10]

Risk Factors

Hypertension was defined when a patient had a resting systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg on repeated measurements during hospitalization or had been using antihypertensive medication. Diabetes mellitus was diagnosed when a patient had a fasting plasma glucose value ≥7 mmol/L or had been treated with an oral hypoglycemic agent or insulin. Hyperlipidemia was diagnosed when a patient had a fasting serum total cholesterol level ≥6.2 mmol/L, low-density lipoprotein cholesterol ≥4.1 mmol/L, or if the patient had been using a lipid-lowering drug after the diagnosis of hyperlipidemia. A current smoker was defined as an individual who smoked at the time of stroke or had quit smoking within 1 year.

Short-Term Functional Outcome and Long-Term Mortality

Short-term functional outcomes at 3 months were determined with the modified Rankin Scale. Poor outcome was defined as an modified Rankin Scale score >2. Long-term mortality and causes of death were identified using death certificates from the Korean National Statistical Office. In Korea, by law, all deaths of Koreans must be reported to the National Statistical Office. Deaths during the hospitalization or within 48 hours after discharge from a hospital are certified by the physician who examined the decedent. For deaths not certified by physicians, any vague or missing item on the death certificate is clarified by the National Statistical Office via telephone.[18] The causes of death in death statistics of the Korean National Statistical Office have been reported to be reliable.[3,19] Deaths among subjects from July 1997 to December 31, 2007, were confirmed by matching the information in the death records and identification numbers assigned to subjects at birth.[20] The cause of death was coded according to the *International Classification of Disease*, 10th revision. Cardiovascular death included fatal stroke (I60–64) and fatal ischemic heart disease caused by myocardial infarction (I21–23, I46).

Standardized Mortality Ratio

We used indirect standardization method and calculated standardized mortality ratio (SMR) to compare the mortality in patients with stroke and the mortality in the general Korean population. The SMR is the ratio of observed number of deaths in the study population to expected number of deaths estimated from the standard population.[21] For the calculation of SMR, we used sex-specific and age-specific mortality data from the entire Korean population in 2003, which was the median year of the study. The SMR >1.0 means that excess deaths occurred in the patient population compared with the general population of same sex and age. Sex-adjusted and age-adjusted SMR with 95% confidence interval (CI) was calculated for overall stroke patients as well as for patients with each stroke subtype. To calculate 95% CI of SMR, the mid-P test with Miettinen modification was used.[22] The SMR per 100000 person-years was also calculated.

Statistical Analysis

SPSS for Windows (version 18.0; SPSS, Chicago, IL) and R package version 2.15.0 (http://www.R-project.org) were used for statistical analysis. The Pearson χ^2 test was used to compare frequencies. For continuous variables, data distributions were examined for normality using the Kolmogorov-Smirnov test. Provided that the data did not deviate from a normal distribution, the mean and standard deviation were calculated and independent sample *t* tests were used for comparisons. For data that were not normally distributed, we reported descriptive statistics as the median and interquartile range (IQR) and compared them using the Mann–Whitney *U* test. Independent predictors for poor outcome at 3 months were determined using the logistic regression analysis. Variables with $P<0.1$ in univariate analysis

Table 1. Demographic Characteristics According to the Stroke Subtypes

	Total 3278 (100)	LAA 811 (24.7)	CE 682 (20.8)	LAC 489 (14.9)	SOD 94 (2.9)	UM 349 (10.6)	UN 696 (21.2)	UI 157 (4.8)	*P**
Age, y									
Mean±SD	63.7±12.1	65.4±10.5	64.6±12.9	62.5±10.6	46.6±16.2	65.6±11.1	62.6±12.0	65.9±12.1	
Median	65 (57–72)	66 (59–73)	66 (57–74)	63 (56–70)	46.5 (34.75–58.5)	66 (59–73.5)	64 (55–71)	66 (58–74.5)	0.040
<60	1054 (32.2)	209 (25.8)	204 (29.9)	171 (35.0)	71 (75.5)	100 (28.7)	256 (36.8)	43 (27.4)	
60–79	1961 (59.8)	541 (66.7)	397 (58.2)	291 (59.5)	22 (23.4)	216 (61.9)	399 (57.3)	95 (60.5)	
≥80	263 (8.0)	61 (7.5)	81 (11.9)	27 (5.5)	1 (1.1)	33 (9.5)	41 (5.9)	19 (12.1)	
Male	2022 (61.7)	528 (65.1)	376 (55.1)	294 (60.1)	56 (59.6)	239 (68.5)	441 (63.4)	88 (56.1)	0.137
Hypertension	2304 (70.3)	603 (74.4)	422 (61.9)	359 (73.4)	35 (37.2)	274 (78.5)	509 (73.1)	102 (65.0)	0.135
Diabetes	1011 (30.8)	309 (38.1)	142 (20.8)	156 (31.9)	11 (11.7)	114 (32.7)	216 (31.0)	63 (40.1)	0.010
Atrial fibrillation	534 (16.3)	0 (0)	422 (61.9)	0 (0)	0 (0)	112 (32.1)	0 (0)	0 (0)	<0.001
Smoking	1282 (39.1)	356 (43.9)	225 (33)	196 (40.1)	36 (38.3)	135 (38.7)	299 (43.0)	35 (22.3)	<0.001
Hyperlipidemia	377 (11.6)	119 (14.7)	65 (9.6)	56 (11.5)	9 (9.8)	46 (13.2)	68 (9.8)	14 (9)	0.314
Initial NIHSS scores	4 (1.25–8)	4 (2–9)	7 (2–15)	3 (1–4)	3 (1–7.5)	3 (1–7)	3 (1–6)	6 (3–17)	<0.001
<2	745 (25.0)	163 (21.6)	122 (19.6)	117 (27.5)	25 (28.1)	85 (25.9)	218 (32.7)	15 (15.8)	
2–5	1225 (41.1)	296 (39.3)	162 (26.0)	272 (64.0)	38 (42.7)	148 (45.1)	282 (42.3)	27 (28.4)	
≥6	1010 (33.9)	295 (39.1)	338 (54.3)	36 (8.5)	26 (29.2)	95 (29.0)	167 (25.0)	53 (55.8)	
Thrombolysis	256 (7.8)	55 (6.8)	123 (18.0)	7 (1.4)	5 (5.3)	25 (7.2)	36 (5.2)	5 (3.2)	0.027
Antithrombotic	3194 (97.4)	793 (97.8)	652 (95.6)	485 (99.2)	90 (95.7)	346 (99.1)	687 (98.7)	141 (89.8)	<0.001
Antiplatelet	2660 (81.1)	737 (90.9)	328 (48.1)	470 (96.1)	65 (69.1)	289 (82.8)	656 (94.3)	115 (73.2)	0.010
Anticoagulant	630 (19.2)	50 (6.2)	397 (58.2)	8 (1.6)	28 (29.8)	111 (31.8)	29 (4.2)	7 (4.5)	<0.001
Statin	1625 (49.6)	436 (53.8)	278 (40.8)	219 (44.8)	43 (45.7)	192 (55.0)	430 (61.8)	27 (17.2)	<0.001
Length of stay, d	8 (6–11)	9 (6–13)	9 (6–14)	6 (5–9)	10 (6–14.25)	8 (6–12)	7 (5–10)	7 (5–15.5)	0.610
<6	794 (24.2)	153 (18.9)	130 (19.1)	194 (39.7)	13 (13.8)	75 (21.5)	181 (26.0)	48 (30.6)	
6–9	1283 (39.1)	307 (37.9)	223 (32.7)	203 (41.5)	33 (35.1)	138 (39.5)	325 (46.7)	54 (34.4)	
≥10	1201 (36.6)	351 (43.3)	329 (48.2)	92 (18.8)	48 (51.1)	136 (39.0)	190 (27.3)	55 (35.0)	

CE indicates cardioembolism; LAA, large artery atherosclerosis; LAC, lacune; NIHSS, National Institute of Health Stroke Scale; SOD, stroke of other determined etiology; UI, stroke of undetermined etiology because of incomplete evaluation; UM, stroke of undetermined etiology because of multiple causes; UN, stroke of undetermined etiology because of negative evaluation.

Data are expressed as the median (interquartile range) or a N (%).

*P values are compared between UI and other stroke subtypes.

were entered into the multivariate model. To compare the long-term mortality according to the TOAST classification, a Kaplan–Meier analysis was used to estimate survival conditions and the log-rank test was used to compare rate estimates. Cumulative death rates within 30 days, 1 year, and 3 years were also calculated. The Cox proportional hazard regression analysis was performed to calculate crude and adjusted hazard ratios with 95% CI. For univariate Cox analysis, the TOAST classification and possible confounding factors including age, sex, hypertension, diabetes, current smoking, hyperlipidemia, and initial National Institutes of Health Stroke Scale scores were compared. Variables with $P<0.1$ in the univariate analyses were entered into the multivariate Cox regression model to identify independent predictors of long-term mortality. Atrial fibrillation was not entered into the multivariate model because atrial fibrillation was exclusively found in patients with cardioembolism or undetermined etiology because of multiple causes. Internal validation of the models was performed by bootstrapping (2000 resampling) and estimation of the concordance index.[23]

Results

Study Patients

During the study period, 3965 patients were admitted and registered in the stroke registry. After excluding patients with transient ischemic attack (n=258), recurrent stroke after the index event (n=196), or missing data (n=233), 3278 patients with their first-ever stroke were enrolled in this study and were followed-up for a median of 3.4 years (IQR, 1.5–5.7). The median age of the patients was 65 years (IQR, 57–72) and 61.7% of the patients were male. Overall, 49.3% were younger than 65 years and 2.6% were older than 85 years. Female patients were older than male patients (67 years and IQR, 60–74.75 vs 63 years and IQR, 55–71; $P<0.001$). The initial median National Institutes of Health Stroke Scale score was 4 (IQR, 1.25–8). The most frequent stroke subtype was undetermined etiology (37%), followed by large artery atherosclerosis (24.7%), cardioembolism (20.8%), lacunar infarction (14.9%), and stroke of other determined etiology (2.9%). Among the undetermined etiologies, negative evaluation was most frequent (21.2%), followed by multiple causes (10.6%) and incomplete evaluation (4.8%).

Demographic characteristics according to the stroke subtype are shown in Table 1. When comparing patients with other stroke subtypes, those with an incomplete evaluation

were older, more frequently had diabetes, and less frequently were current smokers. The initial stroke severity measured by National Institutes of Health Stroke Scale was most severe in patients with cardioembolism, followed by an incomplete evaluation. Patients with an incomplete evaluation were less frequently treated with thrombolysis during admission (P=0.027) and with antithrombotic agents or statin at discharge (antithrombotic, P<0.001; antiplatelet, P=0.01; anticoagulant, P<0.001; and statin, P<0.001) compared with those with the other stroke subtypes.

Evaluation of Stroke Etiology

Angiographic evaluations were performed in 92.4% of all patients. All of the patients with an incomplete evaluation and 13.5% of those with cardioembolism did not undergo a cerebral angiographic study. Echocardiography was performed in 50.6% of patients. Continuous ECG monitoring in the stroke unit or Holter monitoring was performed in 52.2% of patients. Cardiac evaluations were less frequently performed in patients with an incomplete evaluation and none underwent heart CT. Neurosonologic evaluations were also less frequently performed in patients with an incomplete evaluation. The number of patients who were evaluated by at least 1 special cardiac evaluation (echocardiography, continuous ECG monitoring, or heart CT) was lower in cases of incomplete evaluation than in cases of other stroke subtypes (26.8% vs 76.1%; P<0.001; Supplemental Table I).

Functional Outcome at 3 Months

The median length of stay was 8 days (IQR, 6–11). The median length of stay in patients with an incomplete evaluation was not different from that in the other stroke subtypes (7 days and IQR 5–15.5 vs 8 days and IQR 6–11; P=0.610). Among the 3278 patients, data of the modified Rankin Scale at 3 months were available in 3088 patients (overall, 94.2%; 95.7% in large artery atherosclerosis, 95.6% in cardioembolism, 90.6% in lacunar infarction, 93.6% in stroke of other determined etiology, 96.3% in undetermined etiology because of multiple causes, 97.1% in negative evaluation, and 74.5% in incomplete evaluation). Poor outcome was more frequent in patients with an incomplete evaluation than in those with the other stroke subtypes (49.6% vs 24.5%; P<0.001). In contrast, patients with a negative evaluation were more likely to be independent at 3 months (79.7% vs 73.1%; P<0.001). In the multivariate analysis, age, initial stroke severity, discharge medications, and length of stay were independent predictors of poor outcome at 3 months. Among the stroke subtypes, the odds ratio for poor outcome at 3 months was highest in patients with an incomplete evaluation (odds ratio, 3.49; 95% CI, 1.81–6.74; Table 2).

Cumulative Death Rates

During the follow-up period, 781 patients (23.8%) died. Within 30 days, 3.8% of patients died and the overall cumulative death rates were 10.5% within 1 year and 18.4% within 3 years. Among the stroke subtypes, the overall cumulative death rates were highest in patients with an incomplete evaluation (12.7% within 30 days, 25.5% within 1 year, and 35.7% within 3 years), followed by patients with cardioembolism (10.1% within 30 days, 20% within 1 year, and 30.1% within 3 years). In total, 512 patients (15.6%) died because of cardiovascular causes (stroke or ischemic heart disease). Cumulative cardiovascular death rates were 3.3% within 30 days, 7.8% within 1 year, and 12.7% within 3 years. Cumulative cardiovascular death rates were highest in patients with an incomplete evaluation, followed by those with cardioembolism. Among the cases of cardiovascular death, 403 patients (78.7%) died of stroke, whereas 109 (21.3%) patients died of ischemic heart disease. Cumulative rates for fatal stroke within 30 days, 1 year, and 3 years were highest in patients with an incomplete evaluation, whereas cumulative rates for fatal ischemic heart disease within 30 days, 1 year, and 3 years were highest in patients with cardioembolism (Figure 1 and Supplemental Figure II). The Kaplan-Meier survival analysis revealed that more patients with an incomplete evaluation died during long-term follow-up compared with other stroke subtypes (P<0.001; Figure 2A). After excluding early deaths within 30 days, patients with an incomplete evaluation showed still higher long-term mortality (P<0.001; Supplemental Figure III).

Univariate and Multivariate Analyses of Long-Term Mortality

Univariate Cox regression analyses revealed that older age, being female, history of hypertension, atrial fibrillation, not being a current smoker, and initial stroke severity were associated with long-term mortality. Multivariate Cox regression analyses revealed that older age, being female, history of diabetes, and initial stroke severity were associated with long-term mortality. In comparison with lacunar infarction, the risk of long-term death was highest in patients with cardioembolism, followed by those with an incomplete evaluation. Patients with an incomplete evaluation showed a 2.53-fold higher death rate compared with those with lacunar infarction. In contrast, the mortality of patients with a negative evaluation was second lowest after lacunar infarction (Table 3 and Figure 2B). After bootstrapping for internal validation, the concordance index, indicating the probability that the Cox regression model would predict the correct order of survival times of randomly drawn patients was calculated. The concordance index value of 1.0 is equivalent to a perfect prediction, whereas a value of 0.5 corresponds to a coin flip. The concordance index of internal validation models was 0.78 (95% CI, 0.76–0.80), which was very similar to that of current multivariate model (0.78; 95% CI, 0.76–0.81).

Comparison to the Mortality in the General Population

Overall patients with stroke showed significantly higher mortality compared with the general population. Sex-adjusted and age-adjusted SMR was 13.87 (95% CI, 11.61–16.46) for 30 days, 3.39 (95% CI, 3.04–5.62) for 1 year, and 2.26 (95% CI, 2.08–2.45) for 3 years. Among the stroke subtype, patients with stroke of undetermined etiology because of incomplete evaluation showed the highest SMR (49.70 for 30 days, 10.23 for 1 year, and 5.40 for 3 years). Meanwhile, patients with stroke of undetermined etiology because of multiple causes or because of negative evaluation showed

Table 2. Univariate and Multivariate Analysis for Poor Outcome at 3 Months (Modified Rankin Scale Score 3–6)

	Univariate		Multivariate*	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age				
<60	1		1	
60–79	1.82 (1.5–2.22)	<0.001	1.87 (1.46–2.40)	<0.001
≥80	4.73 (3.51–6.37)	<0.001	3.20 (2.19–4.70)	<0.001
Female	1.53 (1.3–1.8)	<0.001	1.22 (0.95–1.57)	0.119
Hypertension	1.09 (0.91–1.3)	0.358		
Diabetes	1.11 (0.93–1.32)	0.234		
Smoking	0.73 (0.62–0.86)	<0.001	0.98 (0.76–1.26)	0.870
Atrial fibrillation	3.05 (2.5–3.71)	<0.001		
Hyperlipidemia	1.13 (0.88–1.45)	0.356		
Initial NIHSS score				
0–2	1		1	
3–6	3.44 (2.27–5.21)	<0.001	3.27 (2.14–5.00)	<0.001
≥7	31.17 (20.94–46.38)	<0.001	22.20 (14.64–33.68)	<0.001
Discharge medication				
Antithrombotic	0.11 (0.06–0.18)	<0.001	0.15 (0.08–0.30)	<0.001
Statin	1.15 (0.98–1.36)	0.084	2.24 (1.80–2.80)	<0.001
Length of stay (d)				
<6	1		1	
6–9	0.95 (0.75–1.21)	0.675	0.97 (0.71–1.33)	0.869
≥10	3.56 (2.85–4.45)	<0.001	2.39 (1.77–3.21)	<0.001
Stroke subtypes				
LAC	1		1	
CE	5.72 (3.97–8.25)	<0.001	1.75 (1.11–2.75)	0.015
LAA	4.1 (2.85–5.9)	<0.001	1.74 (1.12–2.70)	0.014
SOD	2.85 (1.56–5.22)	0.001	2.12 (1.02–4.39)	0.044
UM	3.34 (2.21–5.05)	<0.001	1.83 (1.11–3.02)	0.018
UN	2.63 (1.8–3.84)	<0.001	1.79 (1.14–2.83)	0.012
UI	10.18 (6.24–16.61)	<0.001	3.49 (1.81–6.74)	<0.001

CE indicates cardioembolism; CI, confidence interval; LAA, large artery atherosclerosis; LAC, lacune; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio; SOD, stroke of other determined etiology; UI, stroke of undetermined etiology because of incomplete evaluation; UM, stroke of undetermined etiology because of multiple causes; UN, stroke of undetermined etiology because of negative evaluation.

*Variables (age, sex, smoking, initial NIHSS scores, medications at discharge, length of stay, and stroke subtypes), which showed $P<0.1$ in the univariate analysis, were included in the multivariate analysis.

moderately or slightly increased mortality; SMR of multiple causes was 6.54 for 30 days, 2.33 for 1 year, and 1.92 for 3 years; SMR of negative evaluation was 4.95 for 30 days, 1.80 for 1 year, and 1.36 for 3 years (Table 4).

Discussion

We investigated the long-term mortality and functional outcome at 3 months of stroke patients with undetermined etiologies and showed that the long-term mortality and functional outcome of patients with undetermined etiologies were heterogeneous according to the stroke subtype. Our attention was first drawn to the very high short-term and long-term mortality rates as well as poor functional outcome in patients with an incomplete evaluation.

There are several possible explanations for high mortality in patients with an incomplete evaluation. Patients with an incomplete evaluation might be prone to a higher risk of recurrent stroke, including fatal stroke. Actually, in our study, fatal stroke developed more frequently in the patients with an incomplete evaluation. All patients with an incomplete evaluation did not undergo an angiographic evaluation; therefore, the presence of significant carotid stenosis that might require stent/carotid endarterectomy could be missed. In addition, the presence of intracranial atherosclerosis is associated with higher risks of long-term mortality and stroke recurrence.[24] Lack of those evaluations and treatments in some patients with an incomplete evaluation could result in an increased risk of stroke recurrence and death.

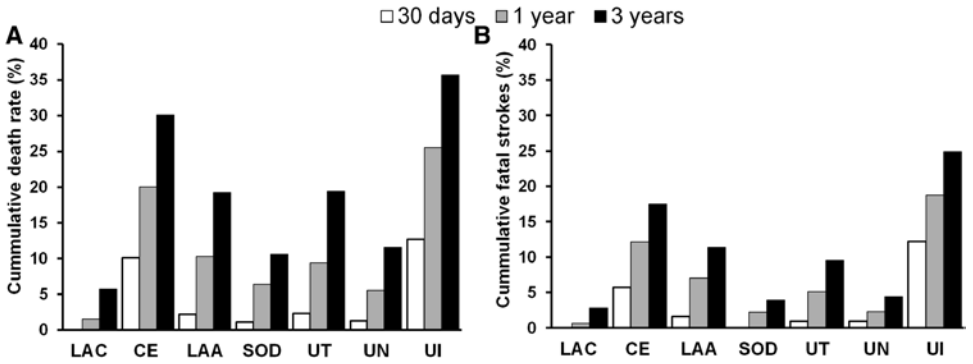

Figure 1. Cumulative death rates according to the stroke subtypes. Overall cumulative death rates (**A**) and cumulative rates for fatal stroke (**B**) within 30 days, 1 year, and 3 years were highest in patients with an incomplete evaluation. LAC, lacune; CE, cardioembolism; LAA, large artery atherosclerosis; SOD, stroke of other determined etiology; UM, stroke of undetermined etiology because of multiple causes; UN, stroke of undetermined etiology because of negative evaluation; UI, stroke of undetermined etiology because of incomplete evaluation; mRS, modified Rankin Scale.

Several studies indicated that higher utilization of tests for stroke evaluation can improve outcomes in acute ischemic stroke patients.[25,26] In our study, only 26.8% of patients with an incomplete evaluation underwent at least 1 special cardiac assessment, whereas 76.1% of the other stroke subtypes underwent at least 1 special cardiac assessment. Detection of cardioembolic sources depends on the depth of cardiac evaluation.[13] Asymptomatic coronary artery atherosclerosis was present in ≈60% to 70% of stroke patients.[16,27] Lack of evaluation for the potential cardiac sources of embolism or failure to detect serious underlying heart diseases such as coronary artery disease might have increased the risk of long-term death.

Another explanation for the higher mortality in patients with incomplete evaluation may be related to the initially severe neurological deficits in these patients. The initial severity of a stroke is one of the major predictors of poor outcome and mortality after the index stroke.[1,28,29] Severe neurological deficits in patients with an incomplete evaluation might lead to poor long-term outcomes. In some patients, the neurological conditions might have been too severe to proceed with an etiologic work-up, which resulted in an incomplete evaluation.

Patients with an incomplete evaluation were less frequently treated with thrombolysis during admission and with antithrombotic agents or statin at discharge compared with those with the other stroke subtypes. Besides appropriate drug treatment and intervention or surgery, lifestyle changes and aggressive risk factor control are essential for preventing cardiovascular events.[30] Although our study did not investigate these factors, it can be assumed that patients with an incomplete evaluation might be less compliant to preventive treatments and might be reluctant to lifestyle changes when considering the fact that many of the patients with an incomplete evaluation were those who refused or were reluctant to undergo stroke evaluation during admission.

In contrast to patients with an incomplete evaluation, the long-term outcomes of patients with negative evaluation were favorable. Patients with a negative evaluation did not have significant large artery atherosclerosis or obvious potential cardiac sources of embolism, which are 2 major etiologies associated with poor outcome. The risk of recurrent stroke in

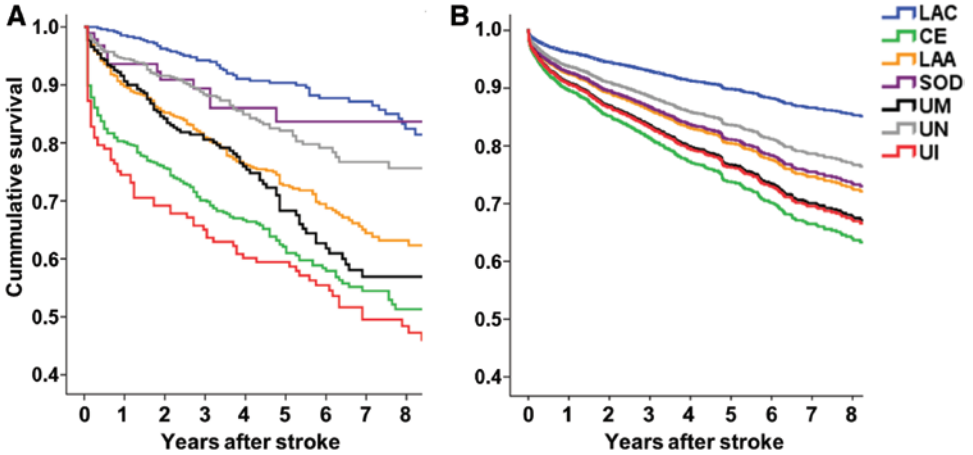

Figure 2. Kaplan–Meier survival curve and Cox regression survival curve according to the stroke subtypes. Univariate Kaplan–Meier survival analysis revealed that more patients with an incomplete evaluation (red) died during follow-up compared with other stroke subtypes ($P<0.001$) (**A**). Multivariate Cox regression curve shows that the risk of long-term death was second highest in patients with an incomplete evaluation (red) after cardioembolism (green) after adjustment of age, sex, hypertension, diabetes, smoking, initial stroke severity, discharge medications, and length of hospital stay (**B**). LAC, lacune; CE, cardioembolism; LAA, large artery atherosclerosis; SOD, stroke of other determined etiology; UM, stroke of undetermined etiology because of multiple causes; UN, stroke of undetermined etiology because of negative evaluation; UI, stroke of undetermined etiology because of incomplete evaluation.

Table 3. Cox Regression Analysis of Long-Term Mortality

	Univariate		Multivariate*	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age (y)				
<60	1		1	
60–79	2.90 (2.37–3.56)	<0.001	2.78 (2.19–3.52)	<0.001
≥80	7.66 (5.97–9.82)	<0.001	6.10 (4.58–8.13)	<0.001
Female)	1.19 (1.03–1.37)	0.016	0.84 (0.70–1.01)	0.064
Hypertension	1.18 (1.01–1.37)	0.042	1.07 (0.90–1.28)	0.423
Diabetes	1.15 (1.00–1.34)	0.059	1.15 (0.98–1.36)	0.096
Atrial fibrillation	3.46 (2.97–4.03)	<0.001		
Smoking	0.75 (0.64–0.87)	<0.001	0.92 (0.76–1.10)	0.288
Hyperlipidemia	0.91 (0.73–1.13)	0.403		
Initial NIHSS score				
0–2	1		1	
3–6	1.67 (1.31–2.12)	<0.001	1.63 (1.28–2.08)	<0.001
≥7	4.49 (3.66–5.49)	<0.001	3.21 (2.57–4.02)	<0.001
Discharge medication				
Antithrombotic	0.17 (0.13–0.22)	<0.001	0.23 (0.17–0.31)	<0.001
Statin	0.67 (0.57–0.79)	<0.001	0.81 (0.68–0.97)	0.019
Length of stay (d)				
<6	1		1	
6–9	0.70 (0.58–0.86)	0.001	0.64 (0.51–0.79)	<0.001
≥10	1.29 (1.07–1.54)	0.007	0.81 (0.65–1.00)	0.052
Stroke subtypes				
LAC	1		1	
CE	4.45 (3.31–5.98)	<0.001	2.84 (2.01–4.02)	<0.001
LAA	2.80 (2.07–3.78)	<0.001	2.03 (1.44–2.86)	<0.001
SOD	1.45 (0.79–2.65)	0.232	1.95 (1.01–3.76)	0.045
UM	3.11 (2.23–4.35)	<0.001	2.48 (1.70–3.61)	<0.001
UN	1.65 (1.19–2.30)	0.003	1.67 (1.16–2.41)	0.006
UI	4.80 (3.38–6.80)	<0.001	2.53 (1.63–3.91)	<0.001

CE indicates cardioembolism; CI, confidence interval; HR, hazard ratio; LAA, large artery atherosclerosis; LAC, lacune; NIHSS, National Institute of Health Stroke Scale; SOD, stroke of other determined etiology; UI, stroke of undetermined etiology because of incomplete evaluation; UM, stroke of undetermined etiology because of multiple causes; UN, stroke of undetermined etiology because of negative evaluation.

*Variables (age, sex, hypertension, diabetes, smoking, initial NIHSS scores, medications at discharge, length of stay, and stroke subtypes), which showed $P<0.1$ in the univariate analysis, were included in the multivariate analysis.

these patients might be lower than that in patients with large artery atherosclerosis or with high-risk cardiac sources of embolism. Moreover, the initial stroke severity in patients with a negative evaluation was mild. These factors might be responsible for the low risk of long-term death in patients with a negative evaluation.

To estimate the risk of long-term mortality according to stroke etiologies compared with a sex-matched and age-matched general Korean population, we calculated the SMR. Poor outcomes of patients with an incomplete evaluation were consistent even after adjustment for sex and age. The SMR within 30 days was almost 50-times higher in patients with an incomplete evaluation.

This study has several limitations. First, although we assumed that higher mortality in patients with an incomplete evaluation was partly attributed to an increased risk of stroke recurrence, we only could obtain the data for fatal strokes. Therefore, based on our data set, we could not determine the actual frequency of all stroke recurrences, including fatal and nonfatal strokes. Second, information on treatment compliance in patients with an incomplete evaluation might have provided a basis for their higher mortality. However, we could not obtain data on treatment compliance for each patient. Third, the definition of an "incomplete evaluation" could differ among studies or physicians. Although we regarded brain CT/magnetic resonance imaging, cerebral angiographic studies, and ECG as essential diagnostic studies, other investigators may consider other additional studies including echocardiographic studies to be essential in some patients. Individualization of definition for "incomplete

Table 4. Population-Adjusted Standardized Mortality Ratio and Rate*

	N of Patients	Observed N of Deaths	Expected N of Deaths	Standardized Mortality Ratio*		Standardized Mortality Rate, Per 100000 Person-Years	
				Estimate	95% CI	Estimate	95% CI
Within 30 d							
All	3278	126	9.08	13.87	11.61–16.46	445.6	367.2–535.3
LAC	489	0	1.15	N/A	N/A	N/A	N/A
CE	682	70	1.66	42.06	33.12–52.96	1308.9	1023.9–1656.2
LAA	811	18	2.73	6.59	4.03–10.22	232.6	126.1–383.6
SOD	94	1	0.09	10.76	0.54–53.03	118.2	–5.6 to 630.3
UM	349	8	1.22	6.54	3.05–12.45	239.8	88.5–495.3
UN	696	9	1.82	4.95	2.41–9.07	126.7	45.3–259.1
UI	157	20	0.40	49.70	31.40–75.85	1674.4	1045.1–2573.3
Within 1 y							
All	3278	342	100.9	3.39	3.04–5.62	81.2	69.5–156.9
LAC	489	7	13.77	0.51	0.22–1.01	–14.1	–22.4 to 0.2
CE	682	136	17.27	7.88	6.63–9.29	211.9	173.6–255.3
LAA	811	83	30.20	2.75	2.20–3.39	71.1	48.9–97.2
SOD	94	6	0.93	6.43	2.61–13.42	57.3	17.0–131.0
UM	349	32	13.71	2.33	1.62–3.26	57.2	26.7–96.6
UN	696	38	21.11	1.80	1.29–2.45	25.8	9.4–46.7
UI	157	40	3.91	10.23	7.41–13.79	290.9	201.9–403.2
Within 3 y							
All	3278	547	242.17	2.26	2.08–2.45	41.0	35.0–47.3
LAC	489	25	36.80	0.68	0.45–0.99	–9.2	–15.8 to –0.3
CE	682	190	40.07	4.74	4.10–5.45	109.3	90.6–130.1
LAA	811	139	70.90	1.96	1.65–2.31	37.0	25.2–50.3
SOD	94	9	1.89	4.76	2.32–8.74	32.0	11.3–65.9
UM	349	59	30.74	1.92	1.47–2.46	36.9	19.0–58.5
UN	696	70	51.59	1.36	1.07–1.70	11.3	2.1–22.4
UI	157	55	10.19	5.40	4.11–6.97	136.6	96.5–185.6

CE indicates cardioembolism; CI, confidence interval; LAA, large artery atherosclerosis; LAC, lacune; NIHSS, National Institute of Health Stroke Scale; SOD, stroke of other determined etiology; UI, stroke of undetermined etiology because of incomplete evaluation; UM, stroke of undetermined etiology because of multiple causes; UN, stroke of undetermined etiology because of negative evaluation.

*The standardized mortality ratio was indirectly adjusted for sex and age, compared with the mortality of the Korean population in 2003.

evaluation" at the physician's own discretion may be subjected to variability of the subtype classification according to the rating physicians even in the similar cases. Therefore, we used a rather simple and uniform definition of essential studies to determine "incomplete evaluation." Fourth, although odds ratio for poor functional outcome at 3 months was highest in patients with an incomplete evaluation among stroke subtypes after adjusting the factors that were significant in univariate analysis, there is a possibility of residual confounding. Fifth, the indirect standardization method controlled sex and age differences between the stroke patients and the general population, but could not control other factors affecting the mortality. Moreover, the SMR of 2 different stroke subtypes could not be directly compared, even though they were calculated in comparison to the same general population. Thus, the SMR should be carefully interpreted as an indicator assessing whether the mortality of patients with a certain stroke subtype is higher or lower than the mortality in a general population of same sex and age.

Conclusions

This study demonstrated that long-term mortality is quite different among stroke patients with undetermined etiology. The mortality was very high in patients for whom the stroke etiology was incompletely evaluated during hospitalization. However, the mortality was low in patients for whom the stroke etiology was not determined despite extensive work-up. Taken together, our findings suggest the importance of initial evaluation for defining the stroke subtype and determining the prognosis.

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Disclosures

None.

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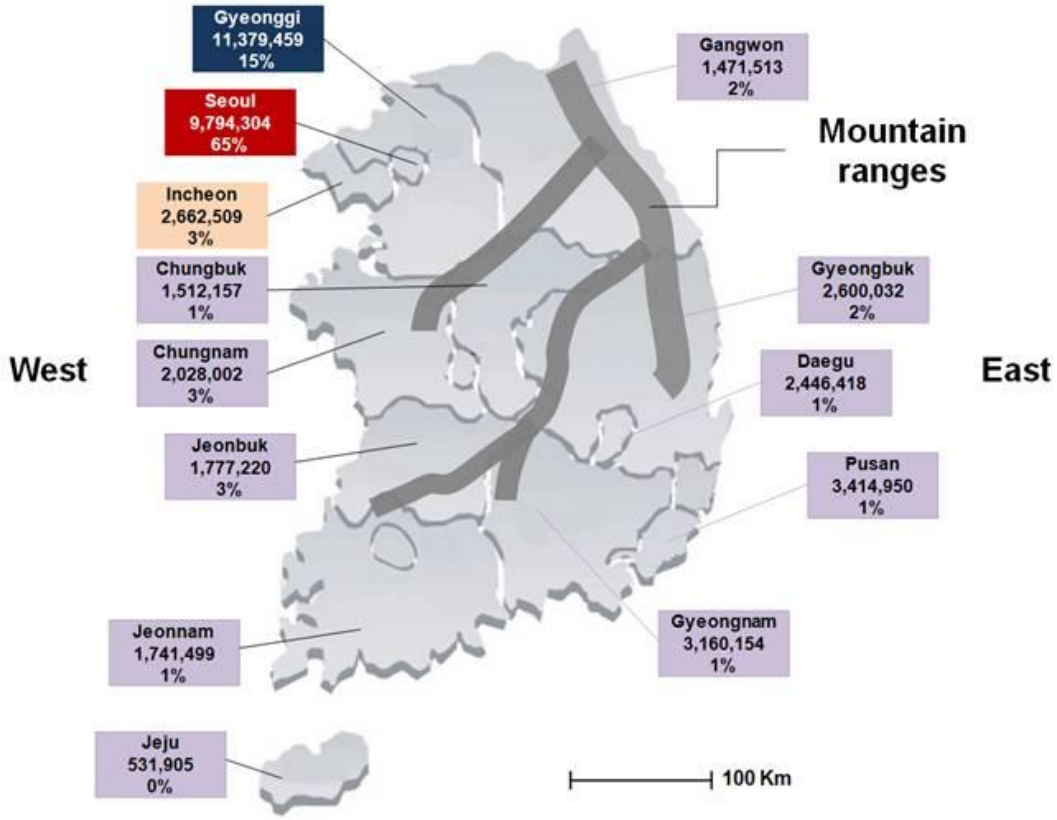
SUPPLEMENTAL MATERIAL

Supplemental Figure 1. The catchment area and population nearby the study hospital.

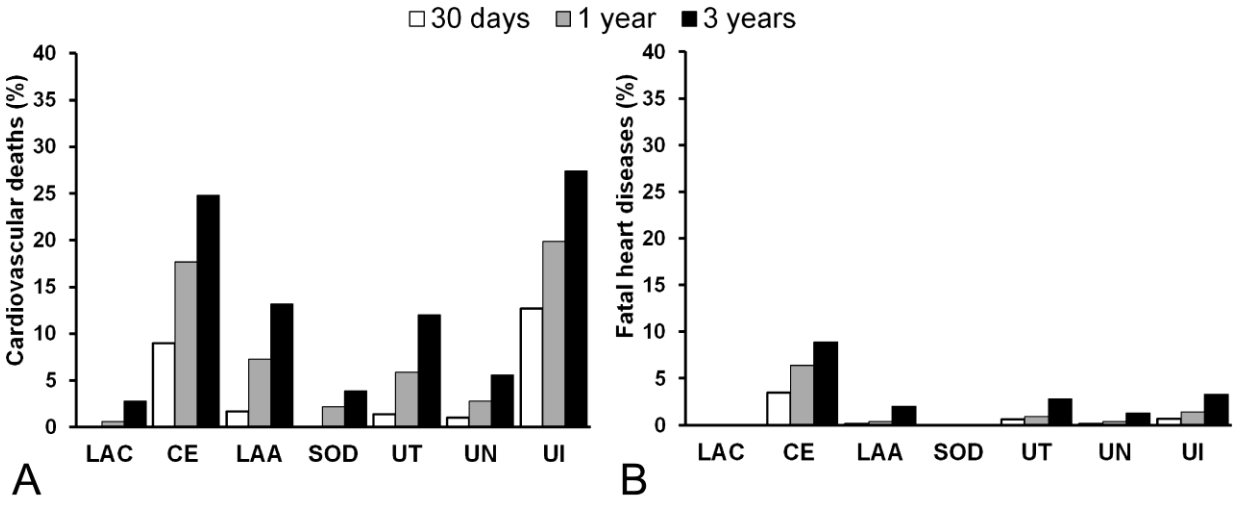
The study hospital is a 2000-bed general hospital located in the western part of Seoul, the capital city of South Korea. About 80% of stroke patients who admit to the study hospital are from Seoul and Gyeonggi province where hold about 20 million inhabitants.



The names of the provinces, number of the population, and the percent of stroke patients who admit to the study hospital are shown in the box.

Supplemental Figure 2. Cumulative death rates according to the stroke subtypes.

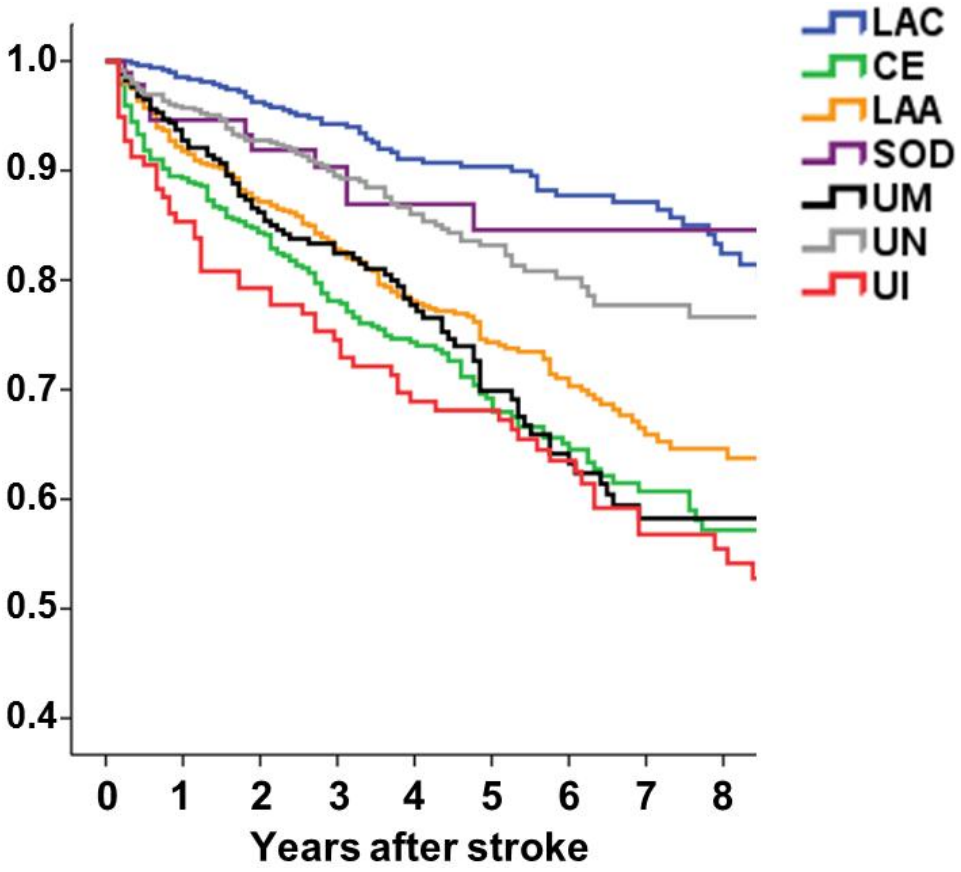
The cumulative cardiovascular death rates (A) and cumulative rates for fatal ischemic heart disease (B) within 30 days, 1 year, and 3 years are shown. The cumulative cardiovascular death rates were highest in patients with an incomplete evaluation. Cumulative rates for fatal ischemic heart disease were highest in patients with cardioembolism.



LAC: lacune, CE: cardioembolism, LAA: large artery atherosclerosis, SOD: stroke of other determined etiology, UM: stroke of undetermined etiology due to multiple causes, UN: stroke of undetermined etiology due to negative evaluation, UI: stroke of undetermined etiology due to incomplete evaluation.

Supplemental Figure 3. Kaplan-Meier Survival curves of the patients who survived for more than 30 days according to the stroke subtypes.

Among the patients who survived for more than 30 days, those with an incomplete evaluation still showed the highest long-term mortality after adjustment of age, sex, hypertension, diabetes, smoking, initial stroke severity, discharge medications, and length of hospital stay.



LAC: lacune, CE: cardioembolism, LAA: large artery atherosclerosis, SOD: stroke of other determined etiology, UM: stroke of undetermined etiology due to multiple causes, UN: stroke of undetermined etiology due to negative evaluation, UI: stroke of undetermined etiology due to incomplete evaluation.

Supplemental Table 1. Etiologic evaluations according to stroke subtypes

	Total	LAA	CE	LAC	SOD	UM	UN	UI	*P**
	3278 (100)	811 (25)	682 (20)	489 (15)	94 (3)	349 (11)	696 (21)	157 (5)	
Angiographic evaluations	3029 (92.4)	811 (100)	590 (86.5)	489 (100)	94 (100)	349 (100)	696 (100)	0 (0)	<0.001
CTA	442 (13.5)	99 (12.2)	126 (18.5)	49 (10.0)	6 (6.4)	50 (14.3)	112 (16.1)	0 (0)	<0.001
MRA	2325 (70.9)	608 (75.0)	425 (62.3)	390 (79.8)	63 (67.0)	264 (75.6)	575 (82.6)	0 (0)	<0.001
DSA	1153 (35.2)	392 (48.3)	236 (34.6)	109 (22.3)	64 (68.1)	132 (37.8)	220 (31.6)	0 (0)	<0.001
Neurosonographic evaluations	1094 (33.4)	307 (37.9)	201 (29.5)	129 (26.4)	35 (37.2)	132 (37.8)	279 (40.1)	11 (7.0)	<0.001
Carotid Doppler	816 (24.9)	207 (25.5)	153 (22.4)	96 (19.6)	25 (26.6)	98 (28.1)	234 (33.6)	3 (1.9)	<0.001
TCD	1076 (32.8)	126 (25.8)	197 (28.9)	126 (25.8)	34 (36.2)	127 (36.4)	277 (39.8)	11 (7.0)	<0.001
Echocardiography	1660 (50.6)	351 (39.1)	447 (65.5)	191 (39.1)	50 (53.2)	243 (69.6)	358 (51.4)	20 (12.7)	<0.001
TEE	1432 (43.7)	319 (39.3)	353 (51.8)	181 (37.0)	41 (43.6)	202 (57.9)	317 (45.5)	19 (12.1)	<0.001
TTE	361 (11.0)	45 (5.5)	166 (24.3)	45 (5.5)	10 (10.6)	64 (18.3)	57 (8.2)	1 (0.6)	<0.001
Continuous ECG monitoring	1712 (52.2)	414 (51)	392 (57.5)	207 (42.3)	48 (51.1)	191 (54.7)	434 (62.4)	26 (16.6)	<0.001
Heart CT	200 (6.1)	55 (6.8)	35 (5.1)	21 (4.3)	5 (5.3)	29 (8.3)	55 (7.9)	0 (0)	0.001
At least one special cardiac evaluation performed†	2417 (73.7)	570 (70.3)	581 (85.2)	300 (61.3)	72 (76.6)	299 (85.7)	553 (79.5)	42 (26.8)	<0.001

* P-values are compared between UI and other stroke subtypes.
†Special cardiac evaluation includes echocardiography, continuous ECG monitoring, and heart CT.

Data are expressed as a number (%). LAA: large artery atherosclerosis, LAC: lacune, CE: cardioembolism, SOD: stroke of other determined etiology, UM: stroke of undetermined etiology due to multiple causes, UN: stroke of undetermined etiology due to negative evaluation, UI: stroke of undetermined etiology due to incomplete evaluation, CTA: CT angiography, MRA: MR angiography, DSA: digital subtraction angiography, TEE: transesophageal echocardiography, TTE: transthoracic echocardiography, ECG: electrocardiography, TCD: transcranial Doppler.